



Molecular Insights into Glyceraldehyde-3-Phosphate Dehydrogenase: A Computational Approach

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ABSTRACT

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (EC 1.2.1.12) is a quintessential enzyme of oxidoreductase class in cellular metabolism. As a moonlighting protein, it performs various metabolic and non-metabolic activities beyond glycolysis, including membrane fusion, cytoskeletal organization, apoptosis regulation, nuclear RNA export, DNA replication and repair, etc. GAPDH is also a Chaperone protein. It is associated with diseases like cancer, diabetes, and neurodegenerative disorders. Research on GAPDH could help in diagnosing and treating these diseases. This enzyme was subjected to a proteomic study on its amino acids sequence, physicochemical characterization, phylogenetic relationship, protein disorder prediction and putative metabolic pathway engineering employing various bioinformatics tools.

INTRODUCTION

- ❖ The most studied structure of GAPDH is homotetramer with quaternary level of organization containing 335 amino acids. The molecular weight of tetramer is nearly 150 kDa with each identical subunits weighing nearly 37 kDa.
- ❖ Its encoding gene, also called GAPDH, a housekeeping gene, is situated on the 12th chromosome of humans.
- ❖ GAPDH mostly found in cytoplasm but to a small extent it is also found in the nucleus, the mitochondria and the small vesicles.

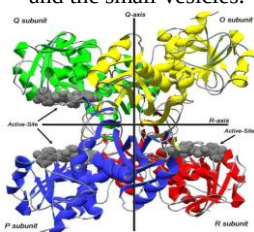


Fig. 1: Human placental GAPDH structure.

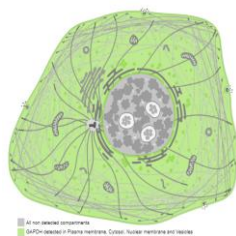


Fig. 2: Sub-cellular location of GAPDH.

OBJECTIVES

1. Exploration and analysis of the high scoring homologous protein sequences of human GAPDH.
2. Physicochemical characterization of GAPDH.
3. Evolutionary relationship among corresponding homologous protein sequences based on GAPDH.
4. Proteomic case study of GAPDH protein.
5. Predicting the protein disorder.
6. Putative metabolic pathway engineering.

METHODOLOGY

Retrieval of protein sequence data using UniProt ID.

BLAST Homology search of selected protein from UniProt.

Physicochemical analysis of GAPDH & its homologous sequences using ProtParam Expaty.

Multiple sequence alignment using ClustalW & phylogenetic trees creation using MEGA11 & its analysis.

Protein disorder prediction using PONDR.

Putative metabolic pathway engineering using BioRender.

RESULT & DISCUSSION

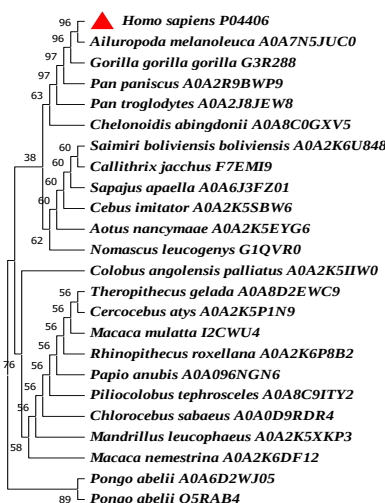


Fig. 3: Phylogenetic tree by maximum parsimony method.

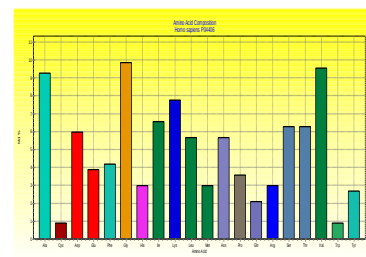


Fig. 4: Amino acids composition histogram of GAPDH by BioEdit.

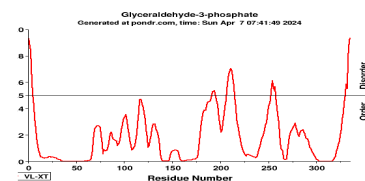


Fig. 5: PONDR score v/s Residue number graph of GAPDH.

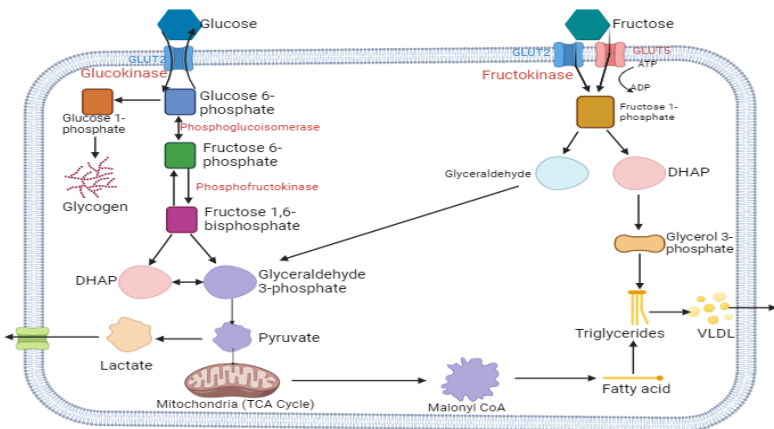


Fig. 6: Putative metabolic pathway engineering of fructose metabolism using BioRender.

- ❖ GAPDH has 335 amino acids with negatively & positively charged residues are 33 & 36 respectively. Molecular weight found to be 36053.21. The most abundant amino acid was found to be Glycine & least abundant were Tryptophan & Cysteine. General formula for NADPH can be written as $C_{1603}H_{2536}N_{440}O_{479}S_{13}$.
- ❖ T.pI was 8.57 indicating GAPDH is basic. Aliphatic index was 84.69 denoting it is thermally stable. Instability index was 15.61 signifying its stability. GRAVY was -0.108 meaning it is hydrophilic & contains more non-polar amino acids.
- ❖ GAPDH of *Homo sapiens* & *Ailuropoda melanoleuca* share common clade indicating more recent common ancestry.
- ❖ The PONDR predicted residue was found to be 335. The number of residues disordered was 28 with overall percentage disordered was 8.36. The numbers of disordered regions were 5. The longest disordered region was 8. The average prediction score was calculated to be 0.1834.

CONCLUSION

GAPDH is implicated in an array of illnesses, including neurological disorders, diabetes and cancer, which emphasizes the necessity of developing therapeutic approaches that specifically target its activity. It's important to comprehend the role of GAPDH in each pathology while also considering its structural features into account when developing drugs that particularly alter its function.

REFERENCES

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